to a restriction or election requirement. Applicants believe this designation of claims 1-18 was a typographical error that requires no reply, as no mention of such the restriction or election is made in the Detail Action.

By this paper, and in view of the amendments above and the following remarks, Applicants respectfully contend that these rejections have been fully replied to and traversed, and that the application is in condition for allowance, which allowance is respectfully requested.

Regarding claim 1, Applicants claim a method for automatically creating crosstalk-corrected data of a microarray. Crosstalk is caused by overlapping dye emission spectra. The method comprises providing a microarray substrate having calibration dye spots. Each of the calibration dye spots comprises a single pure dye. The method further comprises, for each of the calibration dye spots, generating a dye image containing at least one of the calibration dye spots for each of a plurality of output channels. The method still further comprises, for each of the calibration dye spots, measuring an output of each of the output channels to obtain output measurements. The method still further comprises computing a set of correction factors from the output measurements. The method finally comprises applying the set of correction factors to data obtained from microarray images containing spots having dyes with excitation or emission spectra to obtain crosstalk-corrected data.

The Examiner asserts under 35 U.S.C. 102(b) that each element of Applicants' claim 1 is particularly anticipated by *Shalon*, where the Examiner asserts *Shalon* teaches the following:

> Shalon et al. discloses a method of correcting cross-talk between two different flourescent signals in a DNA microarray made on a glass surface and a computerized system thereof. The red and green hybridization intensities are corrected using experimentally determined coefficients. (See in particular abstract; page 642, left column; and detection and analysis

section on page 644.) While the reference does not explicitly refer to calibration dye spots using a single pure dye, the reference appears to correct for cross talk in the same manner as set forth in the specification and as such it is reasonable to infer that single pure dye spots were used for calibration absent evidence to the contrary. Such calibration spots appear to have been routine in the art at the time of the invention. (See at least Schermer et al., U.S. Patent No. 6,075,613, at column 2, lines 20-50.)

Shalon discloses a system for making microarrays of DNA samples on glass substrates, probing them by hybridization with complex flourescent-labeled probes, and using a laser-scanning microscope to detect the fluorescence signals representing hybridization. (Page 639, col. 1.) More particularly, *Shalon* discloses a custom-built laser scanner used to detect two-color fluorescence hybridization signals from arrays. Where the two-color hybridization signals are a combination of red and green hybridization intensities that are corrected for optical crosstalk between fluorescein and lissamine channels, using experimentally determined coefficients. (Page 644, col. 2.)

Shalon does not disclose or define the meaning of "experimental determined coefficients." Rather, *Shalon* merely states that cross-hybridization caused by repetitive sequences can be minimized by prehybridization of the probe or array with vast excess of unlabeled copies of the repetitive sequences. (Page 642, col. 1.) Cross-hybridization is a limitation of the biological assay, namely hybridization, to distinguish similar or related yet nonidentical strands of DNA. *Shalon* describes a means to minimize cross-hybridization artifacts from the gene expression data to optimize the physical and chemical reaction parameters of the hybridization process, namely temperature and salt concentration of the buffers used during hybridization and subsequent washing. This phenomenon is not related to the processes described in Applicants' specification, including fluorescence, dyes, and emission spectra.

In contrast, Applicants, at pages 7-9 of the Specification, clearly provide antecedent basis for their claims to "correction factors" and "crosstalk-correction data." Furthermore, the term "crosstalk" is defined at page 2 which definition is incorporated into each of the independent claims.

Shalon only describes a two-color, two dye microarray and makes not mention of 3, 4, or n-color arrays and their associated crosstalk correction. As such, Applicants' invention provides complexities not even contemplated by *Shalon* in relation to the type of microarray being analyzed .

Moreover, "optical cross-talk" referenced by *Shalon* does not refer to correction of crosstalk caused by overlapping "emission spectra" as claimed by Applicants. Rather *Shalon* refers to correction for purely optical crosstalk produced by his simultaneous specimen illumination scanning structure. (page 644, col. 2).

Based on the foregoing, Applicants respectfully contend that *Shalon* fails to particularly teach each element of Applicants' claimed invention. Both claims 1 and 10 call for a number of steps or elements for determining correction factors from calibration dye spots which are simply not the same as "experimentally determined coefficients". As such, claim 1 is patentable in view of *Shalon*.

Claims 2-9 depend from claim 1, and are therefore patentable for at least the same reasons that claim 1 is patentable. Moreover, these claims recite further limitations, in addition to the limitations recited in claim 1, which render these claims separately patentable.

Independent claim 10, is patentable for at least the same reasons that claim 1 is patentable. The limitations of claim 10 are in accordance with the limitations recited in claim 1, and therefore, claim 10 is patentable for at least the same reasons that claim 1 is patentable.

Claims 11-18 depend from claim 10, and are therefore patentable for at least the same reasons that claim 1 is patentable. Moreover, these claims recite further limitations, in addition for limitations of claim 10, which render these claims separately patentable.

Consequently, and in view of the above amendments and remarks, Applicants respectfully contend that each assertion of the Examiner has been fully replied to and traversed, and that the application is in condition for allowance, which allowance is respectfully requested.

Respectfully submitted,

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Attachment

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for automatically creating crosstalk-corrected data of a microarray wherein crosstalk is caused by overlapping dye emission spectra, the method comprising:

providing a microarray substrate having calibration dye spots, each of the calibration dye spots comprising a single pure dye;

for each of the calibration dye spots, generating a dye image containing at least one of the calibration dye spots for each of a plurality of output channels;

for each of the calibration dye spots, measuring an output of each of the output channels to obtain output measurements;

computing a set of correction factors from the output measurements; and

applying the set of correction factors to data obtained from microarray images containing spots having dyes with excitation or emission spectra to obtain crosstalk-corrected data.

10. (Amended) A system for automatically creating crosstalk-corrected data of a microarray wherein crosstalk is caused by overlapping dye emission spectra, the system comprising:

a microarray substrate having calibration dye spots, each of the calibration dye spots comprising a single pure dye;

an image having a plurality of output channels wherein for each of the calibration dye spots the image generates a dye image containing at least one of the calibration dye spots for each of the output channels;

means for measuring an output of each of the output channels for each of the calibration dye spots to obtain output measurements;

means for computing a set of correction factors from the output measurements; and

means for applying the set of correction factors to data obtained from microarray images containing spots having dyes with excitation or emission spectra to obtain crosstalk-corrected data.